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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/653,961	09/01/2000	Guang-Jer Wu	95-97	5662

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GREENLEE WINNER AND SULLIVAN P C
5370 MANHATTAN CIRCLE
SUITE 201
BOULDER, CO 80303

EXAMINER
RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
1642	16

DATE MAILED: 10/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 09/653,961	Applicant(s) WU, GUANG-JER	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *2,4,5,7-12 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,5,7-12 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 7, 2002 has been entered.

2. The amendment filed on June 7, 2002 in Paper No. 13 is acknowledged and has been entered. Claims 3 and 13-19 have been canceled. Claims 2, 4, 5, and 20 have been amended.

3. The declaration under 37 CFR § 1.132 by Guang-Jer Wu filed June 7, 2002 in Paper No. 15 is acknowledged and has been entered.

4. Claims 2, 4, 5, 7-12, and 20 are pending in the application and are currently under prosecution.

Grounds of Claim Rejections Withdrawn

5. Unless specifically reiterated below, the grounds of rejection set forth in the previous Office actions are withdrawn.

Declaration under 37 CFR § 1.132

6. The declaration under 37 CFR § 1.132 by Guang-Jer Wu has been carefully considered, but fails to provide a showing that is commensurate in scope with the claims and therefore is not regarded as having sufficient merit to overcome the grounds of rejection set forth in this and previous Office actions. The particular reasons are discussed below.

Claim Rejections Maintained and Response to Applicants' Remarks

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 2, 4, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Rubenstein, et al (*Prostate* **14**: 383-388, 1989), as evidenced by Shih, et al (*Cancer Research* **54**: 2514-2520, 1994), Liu, et al (*Hinyokika Kiyo Acta Urologica Japonica* **39**: 439-444, 1993), and the annotation that accompanies the MUC18 amino acid sequence entry (Accession No. P43121) in the Swiss Protein Database (see result 1 of the US-09-653-961-2.rsp search report) for the reason stated in the previous Office actions.

The method of prior art is deemed the same as the method of the claims, absent a showing of any difference.

Applicant has traversed the grounds of rejection under 35 USC § 102(b) set forth in the previous Office actions, arguing, "Rubenstein et al. does not teach how to predict an increased risk for metastasis of a prostate cancer cell based on the expression of the MUC18 coding sequence alone" (page 8, paragraph 2). In reply to Applicant's remarks, the claims are drawn to a method *comprising* measuring and comparing the levels of expression of MUC18. Accordingly, Applicant is relying upon a limitation that is not recited in the claims to suggest a distinction between the invention and the prior art.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious

at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 2, 4, 7, 8-10, 12, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rubenstein, et al (*Prostate* **14**: 383-388, 1989) in view of Liu, et al (*Hinyokika Kiyo Acta Urologica Japonica* **39**: 439-444, 1993), Shih, et al (*Cancer Research* **54**: 2514-2520, 1994), US Patent No. 5,807,978 A, and in further view of US Patent No. 6,057,105 A, and as evidenced the annotation that accompanies the MUC18 amino acid sequence entry (Accession No. P43121) in the Swiss Protein Database (see result 1 of the US-09-653-961-2.rsp search report) for the reason stated in the previous Office Action.

Applicant has traversed the rejection under 35 USC § 103(a), newly arguing that none of the cited references provide a suggestion or the motivation to make and use the invention.

In response to Applicant's argument, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as set forth in the Office action mailed April 9, 2001, Liu, et al teach that the level of expression of the HNK-1/Leu-7 epitope of MUC18/A32 is a valuable prognostic factor associated with prostate cancer cell differentiation. The anti-MUC18 antibody made according to the method of US 5,807,978 A can be used in parallel experiments to confirm the results of the immunoassay, in which the anti-HNK-1 antibody is used to measure the level of expression of the MUC18 coding sequence in prostate cancer cells; accordingly, one of ordinary skill in the art at the time the invention was made would have been motivated to make and use the anti-MUC18 antibody, according to the methods of US 5,807,978 A and Rubenstein, et al, respectively, because confirmation of the data acquired in the immunoassay using anti-

HNK-1 antibody would enable a more accurate assessment of the metastatic potential of a patient's prostate cancer cell and thereby increase the ability of the clinician to successfully intervene in the progress of the disease in the patient. Furthermore, the RT-PCR assay is very sensitive and can be used to detect low levels of expression of the MUC18 coding sequence, but it is well known that Northern analysis is a conventional method than can be used alternatively to RT-PCR to determine the levels of expression of the gene encoding MUC18 in prostate cancer cells. As set forth in the Office action mailed April 9, 2001, one of ordinary skill in the art at the time the invention was made would have been motivated to use either RT-PCR or Northern hybridization to confirm the results of the immunoassay of Rubenstein, et al, and/or US 5,807978 A, because confirmation of the data acquired in the immunoassay by a different method would enable a more accurate assessment of the metastatic potential of a patient's prostate cancer cell and thereby increase the ability of the clinician to successfully intervene in the progress of the disease in the patient.

In summary, Applicant's argument has been carefully considered but not found persuasive. Therefore, the rejection of claims 2, 4, 7-12, and 20 under 35 USC § 103 for the reason stated in the previous Office actions is maintained.

New Grounds of Claim Rejections

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 2, 4, 5, 7-12, and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for predicting whether or not a prostate cancer cell has an increased risk for metastasis than a normal prostate cell, wherein the

method comprises determining and comparing the levels of expression of MUC18 by the prostate cancer cell and the normal prostate cell. According to the claims, the level of expression of MUC18 by the cells positively correlates with increased risk that the cell will metastasize. Therefore, the higher the level of expression of MUC18 by a cell the more probable the cell will metastasize.

Firstly, it is well established that a normal prostate cancer cell will not metastasize, as only cancerous cells metastasize. In other words, it is well known in the art that a prostate cancer cell has an increased risk of metastasis than a normal prostate cell. Therefore, if the invention is to have utility, the claims must be interpreted as a method for determining the risk, or probability that a particular subject's primary prostate tumor will metastasize so that the clinician can assess the need for adjuvant therapy, for example, or perhaps therapy designed to prevent metastasis.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because there is insufficient guidance, direction, and exemplification set forth in the specification to enable the skilled artisan to practice the claimed invention with a reasonable expectation of success without having the need to perform additional, undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

For the reasons set forth in the previous Office actions, the art is highly unpredictable, and the state of the art at the time the application was filed was such that one skilled in the art would not have accepted the assertion that one could predict, or determine the probability that a prostate cancer cell will metastasize by determining that the prostate cancer cell has a higher level of expression of MUC18 than a normal prostate cell. As the specification does not exemplify the claimed method nor provide the guidance that would be necessary to the artisan in order to practice the invention

with a reasonable expectation of success, the artisan could not practice the claimed invention without having to first determine the relationship between the level of expression of a prostate cancer cell relative to a normal prostate cell and the likelihood that the prostate cancer cell will metastasize. Moreover, the specification fails to teach the level at which MUC18 must be expressed by a prostate cancer cell that demarcates the prostate cancer cell at risk of metastasis from the prostate cancer cell not at risk of metastasis. As disclosed in Table 1 of the declaration under 37 CFR § 1.132 by Dr. Wu (Paper No. 15), both normal prostate cells and prostate cancer cells may express MUC18; moreover, the table discloses examples of both normal prostate cells and prostate cancer cells that have been found to express approximately equal levels of MUC18. Therefore, it is evident that merely determining that a prostate cancer cell has a higher level of expression of MUC18 than a normal prostate cell cannot be indicative of the prostate cancer cell's increased risk for metastasis, since some normal cells express the same level of MUC18 as some prostate cancer cells and yet will not metastasize. By the same token, the table discloses examples of prostate cancer cells that are metastatic, or have metastasized, which do not express MUC18, or do not express levels of MUC18 that are higher than the levels expressed by some normal prostate cancer cells. In light of the evidence set forth in the declaration, it is apparent that the skilled artisan could not practice the claimed invention with a reasonable expectation of success without first having to perform additional, undue experimentation, because of the necessity of determining which levels of expression of MUC18 by a prostate cancer cell correspond to what risk that the cell will metastasize to accurately and reliably predict the risk.

Additionally, in reply to the previous Office action, Applicants have submitted together with the declaration under 37 CFR § 1.132 a copy of a publication by Wu, et al (*Prostate* **48**: 305-315, 2001). Wu, et al disclose that three prostate cancer cells lines, i.e., TSU-PR1, DU145, and PC-3 express MUC18, as determined by measurements of the amounts of messenger RNA (mRNA) encoding MUC18 and MUC18; each of which is metastatic in nude mice and invasive *in vitro*. In contrast, Wu, et al disclose that another prostate cancer cell line, namely LNCaP.FGC, which does not metastasize in

nude mice or have invasive capacity *in vitro*, does not express MUC18 (page 311, Table II). However, Wu, et al also disclose that LNCaP.FGC was derived from a metastatic prostate tumor, so evidently the cell line is not representative of the tumor from which it was originally derived. While the lack of expression of MUC18 may account for the lack of the cell line's ability to metastasize *in vivo* or invade an artificial basement membrane *in vitro*, Wu, et al note an alternative explanation proposing that the cell line may have been derived from a small subpopulation of tumor cells that were not metastatic (page 313, column 2). The heterogeneity of tumors is well appreciated in the art; tumors are often composed of a mosaic of cell having different phenotypes, some of which express a particular tumor antigen and others that do not, or some of which are metastatic and other that are not.

As set forth in the previous Office actions, Filshie, et al and Shih, et al, for example, have reported the results of studies that suggest that the level of expression of MUC18 in a cell does not correlate with the cell's metastatic potential. Wu, et al (cited above) note the discrepant results of Shih, et al, and state, "the reason for this discrepancy is not clear" (page 313, column 1). Wu, et al suggest that the discrepant results may have arisen because different protocols were used. Even so, Wu, et al, remark that the discrepancy "may suggest unknown, interesting properties of huMUC18 yet to be revealed" (page 313, column 1). Wu, et al conclude, "[t]he positive correlation of expression of huMUC18 in prostate cancer cells raises the **possibility** that it could be a useful marker for the emergence of pre-malignant, malignant, and metastatic prostatic cancer" (emphasis added); and Wu, et al caution, "[h]uMUC18 may also be implicated as a mediator for metastasis of prostate cancers as seen in melanoma, although this requires further investigation" (page 314, column 1).

In the declaration under 37 CFR §1.132, Dr. Wu states that further studies have been performed, which support the correlation between the level of expression of MUC18 in prostate cancer cells and the ability of the cancer cells to traverse an artificial membrane *in vitro*. Dr. Wu states that LNCaP cells were transfected with a DNA construct that expresses MUC18, and relative to the parental cell line, which lacks the ability to invade the artificial membrane, the transfected cells expressing high levels of

MUC18 were able to traverse the membrane. Additionally, Dr. Wu states that the transfected cells expressing MUC18 formed tumors at anatomical sites remote from the prostate of nude mice into which the cells were injected, while the parental cell line did not. Dr. Wu concludes, "the fact that ectopical expression of MUC18 in LNCaP cells confer the metastatic ability [...] clearly demonstrates that MUC18 plays a critical role in promoting metastasis of the prostate cancer and that MUC18 expression in a prostate cancer cell can be used as a predictor of an increased risk for metastasis of that cancer cell" (page 6, paragraph 2). Nevertheless, as Wu, et al disclose, the cell line to which the declaration refers might not be representative of the tumor from which it was originally derived. In light of the discrepant teachings of other investigators, which were referred to in previous Office actions, including Shih, et al and Filshie, et al, it would be necessary to perform further undue experimentation to have a reasonable expectation of successfully practicing the invention, because it has not been established that the expression of MUC18 is indicative of the ability of prostate tumors cells to metastasize *in vivo*.

Furthermore, as set forth in the previous Office actions, it appears that the invention cannot be practiced using any antibody is produced by immunizing an animal with MUC18 or any antigenic fragment thereof. Supporting this ground of rejection, Wu, et al (cited above) disclose that Putz, et al have reported that two antibodies that bind MUC18 do not bind DU145, PC-3, or LNCaP cells. Contrary to the findings of Putz, et al, which suggest that the prostate cancer cell lines do not express MUC18, the specification discloses that DU145 and PC-3, but not the LNCaP cells express MUC18. Perhaps the antibodies produced by immunizing an animal with the "middle portion" of MUC18, i.e., the fragment of MUC18 consisting of amino acids 211-376 of SEQ ID NO: 2, are able to bind an exposed epitope of MUC18, whereas the antibodies of Putz, et al bind an epitope of MUC18 that is not exposed at the surface of these cells. Whatever the explanation for the discrepancy, it appears that only the antibody disclosed in the instant application could be used to successfully practice the claimed method.

However, Wu, et al further disclose that one of four commercially available anti-MUC18 monoclonal antibodies could be used to detect the presence of MUC18 in

extracts of DU145, TSU-PR1, and PC-3 cells. Consequently, while there, in fact, may be more than one antibody that might be used to practice the claimed invention, one skilled in the art cannot predict which antibodies can be used, and which cannot be. Wu, et al suggest that monoclonal antibodies might generally lack the ability to recognize cognate epitopes of MUC18 in prostate cancer cells (page 312).

In summary, the merit of the declaration under 37 CFR § 1.132 has been fully considered but not found sufficient to overcome the grounds of rejection set forth here and in previous Office actions, because the preponderance of evidence suggests that the skilled artisan given only the benefit of the instant application's disclosure, would not have a reasonable expectation of successfully practicing the claimed invention without having need to perform additional, undue experimentation. Accordingly, the specification fails to meet the requirements set forth under 35 USC § 112, first paragraph.

13. Claims 2, 4, 5, 7-12, and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 20 recites, "for predicting an increased risk for metastasis"; however, there does not appear to be sufficient antecedent basis in the specification for recitation of this phrase in the claims. Therefore, the phrase appears to be new matter and accordingly the recitation of the phrase in the claims appears to violate the written description requirement set forth under 35 USC § 112, first paragraph.

Additionally, there does not appear to be proper support for recitation of the term "a MUC18 coding sequence" in claim 20, since the disclosure does not refer to more than one gene encoding MUC18 and it is not clear that Applicant contemplated a prostate cancer cell expressing any other MUC18 coding sequence than the coding sequence encoding SEQ ID NO: 2.

These matters might be resolved, however, if Applicant were able to point to specific disclosures in the specification that are believed to provide adequate support for recitation of the phrases in the claims.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 2, 4, 5, 7-12, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 4, 5, 7-12, and 20 are indefinite because claim 20 does not recite a positive process step that clearly relates back to the preamble of the claim. Therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention. Amending claim 20 to recite, for example, the phrase "whereby an increased risk for metastasis of the prostate cancer cell is predicted" at the end of the last line of the claim can obviate this ground of rejection.

Claims 2, 4, 5, 7-12, and 20 are vague and indefinite because claim 20 recites the term "increased". The term is a relative term that is not defined by the claim and the specification does not provide a standard for ascertaining the degree to which the claim requires the risk for metastasis to be increased in prostate cancer cells expressing a level of MUC18 that is higher than the level of expression in a normal prostate cell. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Claims 2, 4, 5, 7-12, and 20 are vague and indefinite because claim 20 recites the term "higher". The term is a relative term that is not defined by the claim and the specification does not provide a standard for ascertaining the degree to which the claim requires the level of expression of MUC18 in the prostate cancer cell to be greater than the level of expression of MUC18 in a normal prostate cell so that the prostate cancer cell can be considered to have an increased risk for metastasis. Accordingly, one of

ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
September 30, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600